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(54) Title: TRANSDERMAL DELIVERY OF PEPTIDES

(57) Abstract

The present invention relates to a drug delivery system comprising a transdermal device and, as an active agent, a GHRP (growth hormone releasing peptide).

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Transdermal delivery of peptides

Technical field

The present invention relates to a transdermal drug delivery device. More particularly, this invention relates to electrolytic drug delivery, including iontophoretic drug delivery and still more particularly, but without limitation hereto, this invention relates to the iontophoretic delivery of GHRP (growth hormone releasing peptides) and in particular those peptides disclosed in WO95/17423 and WO97/00894 at therapeutically effective rates.

Background art

Peptides are particularly susceptible to degradation when administered by routes other than parenteral. Non-parenteral administration alternative to intravenous administration of peptide drugs is an area of research.

Due to proteolytic enzymes in the gastro-intestinal tract and extensive "first-pass" hepatic metabolism, peptides are not usually active following oral administration. However, other routes of drug delivery, including transdermal, provide the possibility of avoiding the hepatogastrointestinal "first-pass" elimination and better patient compliance. Because peptides have large molecular weights, are mostly hydrophilic and are often charged, their passive transdermal delivery is possible, and an enhancement strategy is therefore essential. Iontophoresis, which employs an electric potential gradient to drive substances through the skin, represents one approach to increase the skin's permeability.

Iontophoresis, however, has demonstrated wide-spread success in peptide delivery, and has been disclosed in WO 92/07618, WO 92/12999, WO 91/15260 and EP 0 516 026 A1.

Summary of the invention

The present invention is directed to a drug delivery dosage form for transdermal administration of growth hormone releasing peptides.

It has surprisingly been found that therapeutically effective amounts of

compounds of the general formula I

$$A\text{-}B\text{-}C\text{-}D(\text{-}E)_p$$

wherein p is 0 or 1;

A is hydrogen or $R^1\text{-}(CH_2)_q\text{-}(X)_r\text{-}(CH_2)_s\text{-}CO\text{-}$, wherein

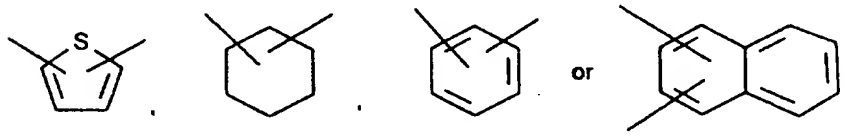
q is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

r is 0 or 1;

s is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

R^1 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino or $N(R^2)\text{-}R^3$, wherein each of R^2 and R^3 is independently hydrogen or lower alkyl optionally substituted by one or more hydroxyl, pyridinyl or furanyl groups; and

X, when r is 1, is -NH-, $-CH_2-$, -CH=CH-, $-C(R^{16})(R^{17})-$,



wherein each of R^{16} and R^{17} is independently hydrogen or lower alkyl;

B is $(G)_t\text{-}(H)_u$ wherein each of t and u independently is 0 or 1;

G and H are amino acid residues selected from the group consisting of natural L-amino acids or their corresponding D-isomers, or non-natural amino acids such as 1,4-diaminobutyric acid, amino-isobutyric acid, 1,3-diaminopropionic acid, 4-aminophenylalanine, 3-pyridylalanine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydronorharman-3-carboxylic acid, N-methylanthranilic acid, anthranilic acid, N-benzylglycine, 3-aminomethylbenzoic acid, 3-amino-3-methyl butanoic acid, sarcosine, nipecotic acid or iso-nipecotic acid;

and wherein, when both t and u are 1, the amide bond between G and H is optionally replaced by $Y\text{-}NR^{18}\text{-}$, wherein Y is -CO- or $-CH_2-$, and R^{18} is hydrogen, lower alkyl or lower aralkyl;

C is a D-amino acid of formula $-NH\text{-}CH((CH_2)_w\text{-}R^4)\text{-}CO\text{-}$ wherein

w is 0, 1 or 2; and

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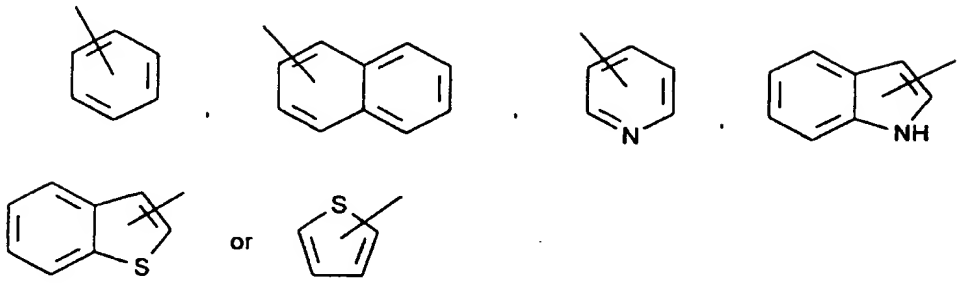
R^4 is selected from the group consisting of



each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, lower alkylamino, amino or hydroxy;

D, when p is 1, is a D-amino acid of formula

$-NH-CH((CH_2)_k-R^5)-CO-$

or, when p is 0, D is $-NH-CH((CH_2)_l-R^5)-CH_2-R^6$

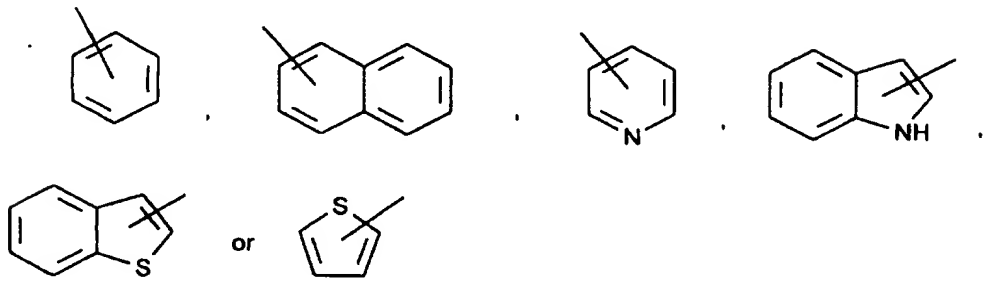
or $-NH-CH((CH_2)_m-R^5)-CO-R^6$, wherein

k is 0, 1 or 2;

l is 0, 1 or 2;

m is 0, 1 or 2;

R^5 is selected from the group consisting of



each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy amino or hydroxy; and

R^6 is piperazino, morpholino, piperidino, -OH or $-N(R^7)-R^8$, wherein each of R^7 and R^8 is independently hydrogen or lower alkyl;

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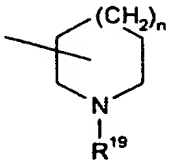
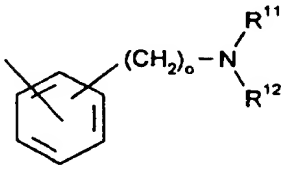
E, when p is 1, is -NH-CH(R^{10})-(CH_2)$_v$-R^9, wherein

v is 0 or an integer selected from the group: 1, 2, 3, 4, 5, 6, 7, 8;

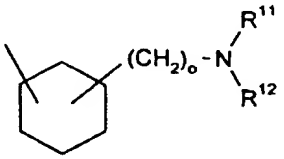
R^9 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino, -N(R^{11})-R^{12}, or



wherein n is 0, 1 or 2, and R^{19} is hydrogen or lower alkyl,

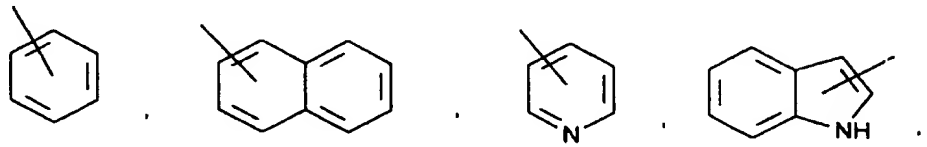


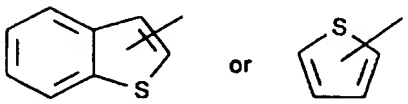
or



wherein o is an integer selected from the group: 1, 2, 3,

each of R^{11} and R^{12} is independently hydrogen or lower alkyl, or





each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, amino, alkylamino, hydroxy, or the Amadori rearrangement product from an amino group and a hexapyranose or a hexapyranosyl-hexapyranose and

R^{10}, when p is 1, is selected from the group consisting of -H, -COOH,

-CH_2-R^{13},

-CO-R^{13} or -CH_2-OH, wherein

R^{13} is piperazino, morpholino, piperidino, -OH or -N(R^{14})-R^{15}, wherein each of

R^{14} and R^{15} is independently hydrogen or lower alkyl;

all amide bonds within formula I, that is, between A and B, including G and H, B and C, C and D and D and E may independently be replaced by $-Y-NR^{18}-$, wherein Y is -CO- or $-CH_2-$, and R^{18} is hydrogen, lower alkyl or lower aralkyl; or a pharmaceutically acceptable salt thereof, may be administered by the transdermal rute.

In one embodiment of the drug delivery system according to the invention, the compound of formula I is selected from growth hormone releasing peptides having 3-10 amino acids, such as 3, 4, 5, 6, 7, 8, 9 or 10 amino acids, preferably 3-9, more preferred 4-8, still more preferred 4-6, and most preferred 5 amino acids, or pharmaceutically acceptable salts thereof.

In another embodiment of the drug delivery system according to the invention, at least one of the amino acids, such as 1 to 5, preferably 1, 2, 3 or 4 are selected from the group consisting of D-2Nal, D-Phe, Aib, His, Aib-His, Ala, D-Ala, Ala-His, D-Ala-His, AMB, nipecotic acid or isonipecotic acid.

In a further embodiment of the drug delivery system according to the invention A is selected from Aib or 3-AMB, preferably Aib.

In a still further embodiment of the drug delivery system according to the invention G is selected from Ala, 3-aminomethylbenzoyl, R-nipecotinyl, nipecotic acid or isonipecotic acid or G is absent, preferably G is Ala or absent, more preferred G is absent.

In a further embodiment of the drug delivery system according to the invention H is selected from His or Ala, preferably His.

In a still further embodiment of the drug delivery system according to the invention C is selected from D-2Nal, D-Phe or N-Me-D-Phe, preferably D-2Nal.

In a further embodiment of the drug delivery system according to the invention D is selected from D-Phe, D-2Nal or N-Me-D-Phe, preferably D-Phe.

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In a still further embodiment of the drug delivery system according to the invention E is selected from Lys-NH_2, D-Lys-NH_2, Lys-OH, D-Lys-OH, Gly-NH_2, Orn-NH_2 or Ser-NH_2, preferably Lys-NH_2, D-Lys-NH_2, Lys-OH, D-Lys-OH or Ser-NH_2, more preferably Lys-NH_2, D-Lys-NH_2 or Ser-NH_2.

Particularly preferred compounds of formula I to be used as active agent in the drug delivery system are selected from the group consisting of

H-Ala-Hisy(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-His-D-2Nal-D-Phe-Lys-NH_2,
(3-(4-Imidazolyl)propionyl)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Lys-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-His-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-D-2Nal-D-Phe-Lys-NH_2,
(n-Propyl)-His-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-3Pyal-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Phe(4-NH_2)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-His-D-2Nal-D-Phe-Lys-NH_2,
(2-(4-Imidazolyl)acetyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-(4-Imidazolyl)acryloyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-Aminomethyl benzoyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,
(4-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-Aminocrotonoyl)-D-2Nal-D-Phe-Lys-NH_2,
(4-Piperidino-carboxyl)-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-His-D-2Nal-D-Phe-NH_2,
(H-Ala-His-D-2Nal-D-Phe-NH)hexane,
6-(H-Ala-His-D-2Nal-D-Phe-NH)hexylamine,
5-(H-Ala-His-D-2Nal-D-Phe-NH)pentylanaine,
H-Ala-His-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,
H-Ala-His-D-2Nal-D-Phe-Lys-OH,

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(2S)-(H-Ala-His-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2-(H-Ala-His-D-2Nal-D-Phe-NH)ethyl)benzene,

2-(H-Ala-His-D-2Nal-D-Phe-NH)ethylamine,

4-((H-Ala-His-D-2Nal-D-Phe-NH)methyl)benzylamine

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

H-Ala-His-D-2Nal-D-Phe-Phe-NH_2,

H-Ala-His-D-2Nal-D-Phe-D-Phe-NH_2,

H-Ala-His-D-Phe-D-Phe-Lys-NH_2,

H-Ala-His-D-Trp-D-Phe-Lys-NH_2,

H-His-D-2Nal-D-Trp-Lys-NH_2,

H-Ala-His-D-1Nal-D-Phe-Lys-NH_2,

H-Ala-Phe-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

(2R)-(H-Ala-His-D-2Nal-D-Phe-Lys-NH)-3-phenylpropylamine,

H-Ala-N-Me-(2-aminobenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(Methylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-(Aminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-His-Ala-D-2Nal-D-Phe-Lys-NH_2,

4-(H-Ala-His-D-2Nal-D-Phe-NH)butylamine,

3-(H-Ala-His-D-2Nal-D-Phe-NH)propylamine,

(3-(Dimethylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-hPhe-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)y(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-hPhe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Bzl-Gly-Lys-NH_2,

(2S)-(3-aminomethylbenzoyl)y(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2S)-((3-aminomethylbenzoyl)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-Thial-Lys-NH_2,

(2S)-(H-Aib-Hisy(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-3Pyal-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-F)-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-OMe)-Lys-NH_2,

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(2-Aminomethylphenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(2-Aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Phe-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Hisy(CH_2NH)-D-2Nal-D-Phe-Lys-OH,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Gly-NH_2,

H-Aib-His-D-2Nal-D-Phe-Ala-NH_2,

H-Aib-His-D-2Nal-D-Phe-Orn-NH_2,

(5-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-D-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Dab-NH_2,

H-Aib-His-D-2Nal-D-Phey(CH_2NH)-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-N-Me-Lys-NH_2,

(3-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Lys-$N(Me)_2$,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-1Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Trp-Lys-NH_2,

(Furfuryl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(2-Pyridylmethyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-3Pyal-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(2-(H-Aib-His-D-2Nal-NH)ethyl)benzene,

N,N-di(2R-Hydroxypropyl)-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(2R-Hydroxypropyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,

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(3-Aminomethylbenzoyl)-N-Me-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe-N-Me-Lys-NH_2,

H-D-Thr-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Hyp-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phey(CH_2N(Me))Lys-NH_2,

3-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

3-((Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

3-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

H-Aib-His-D-2Nal-N-Me-D-Phe-Hyp-NH_2,

2-((3-Aminomethylbenzoyl)-
D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-((3R)Piperidinecarbonyl-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane;

2(R)-2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me)-3-phenylpropanol,

3-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-
dimethylaminopropane,

3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-
N,N-dimethylaminopropane,

3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

H-Aib-His-D-2Nal-N-Me-D-Phe-Ser-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH_2,

(4-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,

((3R)-3-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,

(3-Aminomethylbenzoyl)-D-Phe-N-Me-D-Phe-NH_2,

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(3-Aminomethylbenzoyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2

((3R)-3-Piperidinecarbonyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

(2R)-2-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me)-3-(2-naphthyl)propanol,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

3-((3-Aminomethylbenzoyl)-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

(3-aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-Ala-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-Me-D-Phe-NH_2,

2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-morpholinoethane,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH-Me,

3-((3-Methylaminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-N-Me_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

H-3-Aminomethylbenzoyl-N-Me-D-2Nal-N-Me-D-Phe-NH-CH_3,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NHMe,

and Piperidine-4-carboxylic acid-N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoy)-2-(2-naphthyl)ethyl)-N-methylamide,

or a pharmaceutically acceptable salt thereof, such as the benzylate, hydrobromide, citrate, sodium, potassium, calcium, zinc, magnisium, meglumine, acetate, benzoate, fumarate, phosphate, malate, maleate, mandelate, mesylate, lactate, salicylate, sulphate, tartrate, succinate, hydrochloride or TFA salt, as well as the hydrates.

The present invention also relates to a method for transdermal delivery of a growth hormone releasing compound characterized in that said compound has the general formula I

$$A\text{-}B\text{-}C\text{-}D(\text{-}E)_p \quad (I)$$

wherein p is 0 or 1;

A is hydrogen or $R^1\text{-}(CH_2)_q\text{-}(X)_r\text{-}(CH_2)_s\text{-}CO\text{-}$, wherein

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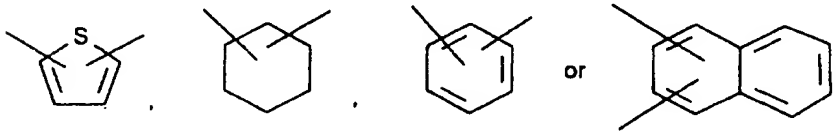
q is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

r is 0 or 1;

s is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

R^1 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino or $N(R^2)$-R^3, wherein each of R^2 and R^3 is independently hydrogen or lower alkyl optionally substituted by one or more hydroxyl, pyridinyl or furanyl groups; and

X, when r is 1, is -NH-, $-CH_2-$, -CH=CH-, $-C(R^{16})(R^{17})-$,



wherein each of R^{16} and R^{17} is independently hydrogen or lower alkyl;

B is $(G)_t$-$(H)_u$ wherein each of t and u independently is 0 or 1;

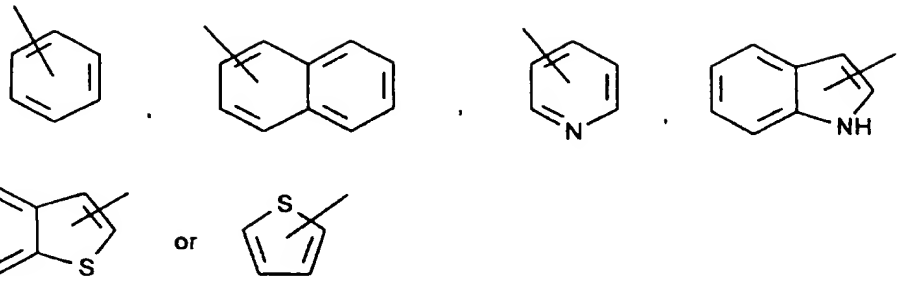
G and H are amino acid residues selected from the group consisting of natural L-amino acids or their corresponding D-isomers, or non-natural amino acids such as 1,4-diaminobutyric acid, amino-isobutyric acid, 1,3-diaminopropionic acid, 4-aminophenylalanine, 3-pyridylalanine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydronorharman-3-carboxylic acid, N-methylanthranilic acid, anthranilic acid, N-benzylglycine, 3-aminomethylbenzoic acid, 3-amino-3-methyl butanoic acid, sarcosine, nipecotic acid or iso-nipecotic acid;

and wherein, when both t and u are 1, the amide bond between G and H is optionally replaced by $Y-NR^{18}-$, wherein Y is -CO- or $-CH_2-$, and R^{18} is hydrogen, lower alkyl or lower aralkyl;

C is a D-amino acid of formula $-NH-CH((CH_2)_w-R^4)-CO-$ wherein

w is 0, 1 or 2; and

R^4 is selected from the group consisting of



each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, lower alkylamino, amino or hydroxy;

D, when p is 1, is a D-amino acid of formula

-NH-CH($(CH_2)_k$-R^5)-CO-

or, when p is 0, D is -NH-CH($(CH_2)_l$-R^5)-CH_2-R^6

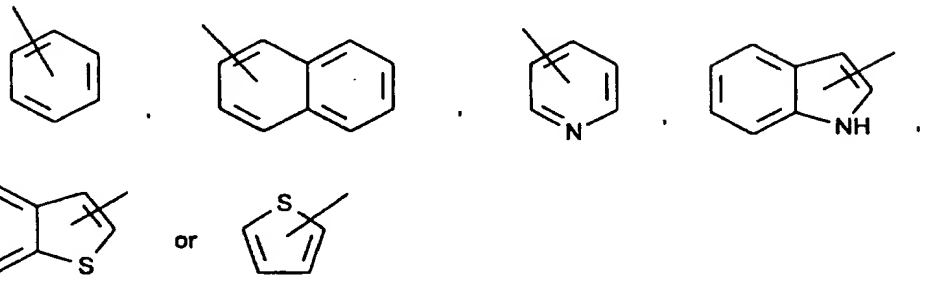
or -NH-CH($(CH_2)_m$-R^5)-CO-R^6, wherein

k is 0, 1 or 2;

l is 0, 1 or 2;

m is 0, 1 or 2;

R^5 is selected from the group consisting of



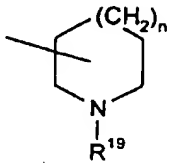
each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy amino or hydroxy; and

R^6 is piperazino, morpholino, piperidino, -OH or -N(R^7)-R^8, wherein each of R^7 and R^8 is independently hydrogen or lower alkyl;

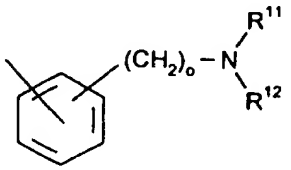
E, when p is 1, is -NH-CH(R^{10})-(CH_2)$_v$-R^9, wherein

v is 0 or an integer selected from the group: 1, 2, 3, 4, 5, 6, 7, 8;

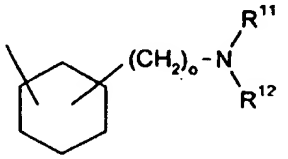
R^9 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino, -N(R^{11})-R^{12}, or



wherein n is 0, 1 or 2, and R^{19} is hydrogen or lower alkyl,

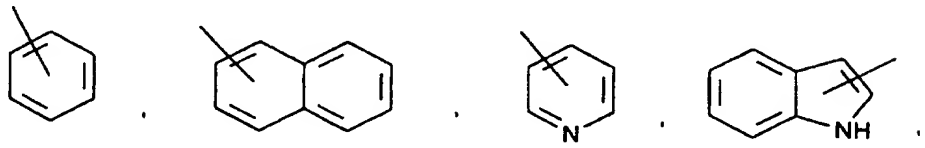


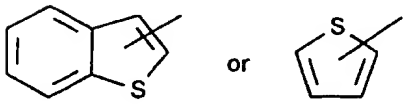
or



wherein o is an integer selected from the group: 1, 2, 3,

each of R^{11} and R^{12} is independently hydrogen or lower alkyl, or





or

each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, amino, alkylamino, hydroxy, or the Amadori rearrangement product from an amino group and a hexapyranose or a hexapyranosyl-hexapyranose and

R^{10}, when p is 1, is selected from the group consisting of -H, -COOH,

-CH_2-R^{13},

-CO-R^{13} or -CH_2-OH, wherein

R^{13} is piperazino, morpholino, piperidino, -OH or -N(R^{14})-R^{15}, wherein each of R^{14} and R^{15} is independently hydrogen or lower alkyl;

all amide bonds within formula I, that is, between A and B, including G and H, B and C, C and D and D and E may independently be replaced by -Y-NR^{18}-, wherein Y is -CO- or -CH_2-, and R^{18} is hydrogen, lower alkyl or lower aralkyl; or a pharmaceutically acceptable salt thereof.

In one embodiment of the above method the compound of formula I is selected from growth hormone releasing peptides having 3-10 amino acids, preferably 3-9, more preferred 4-8, still more preferred 4-6, and most preferred 5 amino acids, or pharmaceutically acceptable salts thereof.

In another embodiment of the above method, at least one of the amino acids are selected from the group consisting of D-2Nal, D-Phe, Aib, His, Ala, D-Ala, AMB, nipecotic acid or iso-nipecotic acid.

In a further embodiment of the above method the peptide of formula I is selected from the group consisting of

H-Ala-Hisψ(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-His-D-2Nal-D-Phe-Lys-NH_2,
(3-(4-Imidazolyl)propionyl)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Lys-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-His-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-D-2Nal-D-Phe-Lys-NH_2,
(n-Propyl)-His-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-3Pyal-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Phe(4-NH_2)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-His-D-2Nal-D-Phe-Lys-NH_2,
(2-(4-Imidazolyl)acetyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-(4-Imidazolyl)acryloyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-Aminomethyl benzoyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,
(4-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

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(3-Aminocrotonoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-Piperidino-carboxyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-NH_2,

(H-Ala-His-D-2Nal-D-Phe-NH)hexane,

6-(H-Ala-His-D-2Nal-D-Phe-NH)hexylamine,

5-(H-Ala-His-D-2Nal-D-Phe-NH)pentylanaine,

H-Ala-His-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys-OH,

(2S)-(H-Ala-His-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2-(H-Ala-His-D-2Nal-D-Phe-NH)ethyl)benzene,

2-(H-Ala-His-D-2Nal-D-Phe-NH)ethylamine,

4-((H-Ala-His-D-2Nal-D-Phe-NH)methyl)benzylamine ,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

H-Ala-His-D-2Nal-D-Phe-Phe-NH_2,

H-Ala-His-D-2Nal-D-Phe-D-Phe-NH_2,

H-Ala-His-D-Phe-D-Phe-Lys-NH_2,

H-Ala-His-D-Trp-D-Phe-Lys-NH_2,

H-His-D-2Nal-D-Trp-Lys-NH_2,

H-Ala-His-D-1Nal-D-Phe-Lys-NH_2,

H-Ala-Phe-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

(2R)-(H-Ala-His-D-2Nal-D-Phe-Lys-NH)-3-phenylpropylamine,

H-Ala-N-Me-(2-aminobenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(Methylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-(Aminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-His-Ala-D-2Nal-D-Phe-Lys-NH_2,

4-(H-Ala-His-D-2Nal-D-Phe-NH)butylamine,

3-(H-Ala-His-D-2Nal-D-Phe-NH)propylamine,

(3-(Dimethylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-hPhe-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)y(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-hPhe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Bzl-Gly-Lys-NH_2,

(2S)-(3-aminomethylbenzoyl)ψ(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2S)-((3-aminomethylbenzoyl)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-Thial-Lys-NH_2,

(2S)-(H-Aib-Hisψ(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-3Pyal-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-F)-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-OMe)-Lys-NH_2,

(2-Aminomethylphenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(2-Aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Phe-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Hisψ(CH_2NH)-D-2Nal-D-Phe-Lys-OH,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Gly-NH_2,

H-Aib-His-D-2Nal-D-Phe-Ala-NH_2,

H-Aib-His-D-2Nal-D-Phe-Orn-NH_2,

(5-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-D-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Dab-NH_2,

H-Aib-His-D-2Nal-D-Pheψ(CH_2NH)-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-N-Me-Lys-NH_2,

(3-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Lys-N$(Me)_2$,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-1Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Trp-Lys-NH_2,

(Furfuryl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(2-Pyridylmethyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-3Pyal-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(2-(H-Aib-His-D-2Nal-NH)ethyl)benzene,

N,N-di(2R-Hydroxypropyl)-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(2R-Hydroxypropyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Pheψ(CH_2NH)Lys-NH_2,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe-N-Me-Lys-NH_2,

H-D-Thr-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Hyp-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Pheψ(CH_2N(Me))Lys-NH_2,

3-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

3-((Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

3-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

H-Aib-His-D-2Nal-N-Me-D-Phe-Hyp-NH_2,

2-((3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-((3R)Piperidinecarbonyl-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane;

2(R)-2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me)-3-phenylpropanol,

3-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

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3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,
3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,
H-Aib-His-D-2Nal-N-Me-D-Phe-Ser-NH_2,
(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH_2,
(4-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,
((3R)-3-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,
(3-Aminomethylbenzoyl)-D-Phe-N-Me-D-Phe-NH_2,
(3-Aminomethylbenzoyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2
((3R)-3-Piperidinecarbonyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,
((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
(2R)-2-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me)-3-(2-naphthyl)propanol,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
3-((3-Aminomethylbenzoyl)-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
(3-aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,
H-Aib-Ala-D-2Nal-N-Me-D-Phe-Lys-NH_2,
H-Aib-His-D-2Nal-N-Me-D-Phe-NH_2,
2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-morpholinoethane,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH-Me,
3-((3-Methylaminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-imethylaminopropane,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-N-Me_2,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
H-3-Aminomethylbenzoyl-N-Me-D-2Nal-N-Me-D-Phe-NH-CH_3,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NHMe,
and Piperidine-4-carboxylic acid-N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,
or a pharmaceutically acceptable salt thereof.

In a further embodiment of the above method the pharmaceutically acceptable salt is the besylate, hydrobromide, citrate, sodium, potassium, calcium, zinc, magnisium, meglumine, acetate, benzoate, fumarate, phosphate, malate, maleate, mandelate, mesylate, lactate, salicylate, sulphate, tartrate, succinate, TFA, hydrochloride and/or hydrate salt.

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In a preferred embodiment of the above method the transdermal device is a iontophoretic device.

In a further embodiment of the above method the drug delivery system further comprises a hydrogel.

In a further embodiment of the above method the transdermal device comprises a dry-state assembly.

In a further embodiment of the above method the compound is delivered in an amount of from about 0.001 mg to about 10 mg per subject per day.

The present invention further relates to use of a compound of the general formula I

$$A\text{-}B\text{-}C\text{-}D(\text{-}E)_p \quad (I)$$

wherein p is 0 or 1;

A is hydrogen or $R^1\text{-}(CH_2)_q\text{-}(X)_r\text{-}(CH_2)_s\text{-}CO\text{-}$, wherein

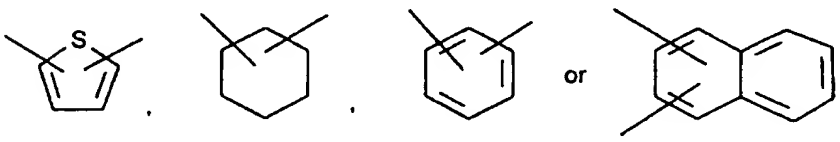
q is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

r is 0 or 1;

s is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

R^1 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino or $N(R^2)\text{-}R^3$, wherein each of R^2 and R^3 is independently hydrogen or lower alkyl optionally substituted by one or more hydroxyl, pyridinyl or furanyl groups; and

X, when r is 1, is -NH-, $-CH_2-$, -CH=CH-, $-C(R^{16})(R^{17})-$,

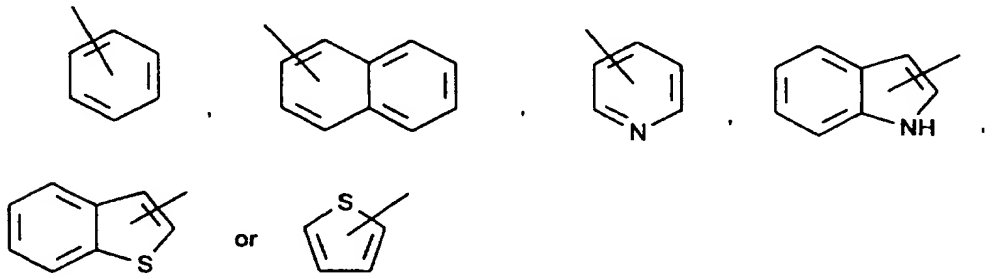


wherein each of R^{16} and R^{17} is independently hydrogen or lower alkyl;

B is $(G)_t\text{-}(H)_u$ wherein each of t and u independently is 0 or 1;

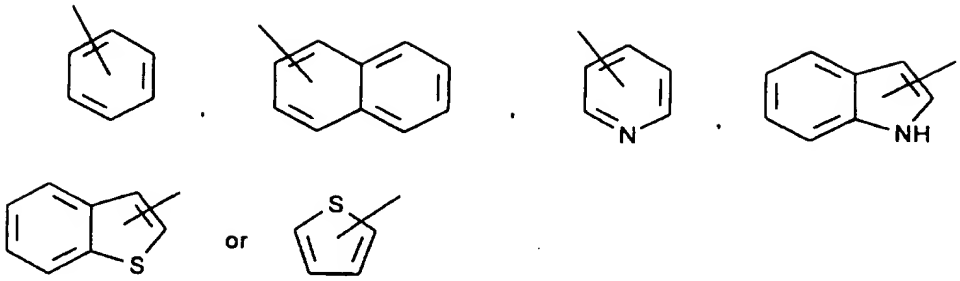
G and H are amino acid residues selected from the group consisting of natural L-amino acids or their corresponding D-isomers, or non-natural amino acids such as 1,4-diaminobutyric acid, amino-isobutyric acid, 1,3-diaminopropionic acid, 4-aminophenylalanine, 3-pyridylalanine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydronorharman-3-carboxylic acid, N-methylanthranilic acid, anthranilic acid, N-benzylglycine, 3-aminomethylbenzoic acid, 3-amino-3-methyl butanoic acid, sarcosine, nipecotic acid or iso-nipecotic acid;
and wherein, when both t and u are 1, the amide bond between G and H is optionally replaced by Y-NR^{18}-, wherein Y is -CO- or -CH_2-, and R^{18} is hydrogen, lower alkyl or lower aralkyl;

C is a D-amino acid of formula -NH-CH($(CH_2)_w$-R^4)-CO- wherein
w is 0, 1 or 2; and
R^4 is selected from the group consisting of



each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, lower alkylamino, amino or hydroxy;

D, when p is 1, is a D-amino acid of formula
-NH-CH($(CH_2)_k$-R^5)-CO-
or, when p is 0, D is -NH-CH($(CH_2)_l$-R^5)-CH_2-R^6
or -NH-CH($(CH_2)_m$-R^5)-CO-R^6, wherein
k is 0, 1 or 2;
l is 0, 1 or 2;
m is 0, 1 or 2;
R^5 is selected from the group consisting of



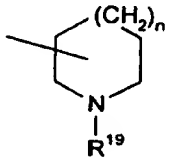
each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy amino or hydroxy; and

R^6 is piperazino, morpholino, piperidino, -OH or -N(R^7)-R^8, wherein each of R^7 and R^8 is independently hydrogen or lower alkyl;

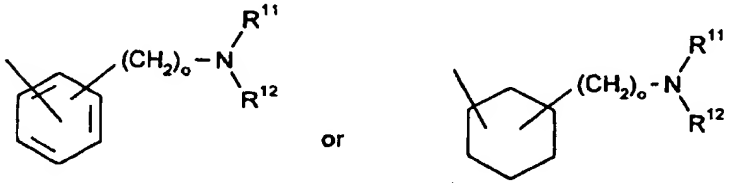
E, when p is 1, is -NH-CH(R^{10})-$(CH_2)_v$-R^9, wherein

v is 0 or an integer selected from the group: 1, 2, 3, 4, 5, 6, 7, 8;

R^9 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino, -N(R^{11})-R^{12}, or

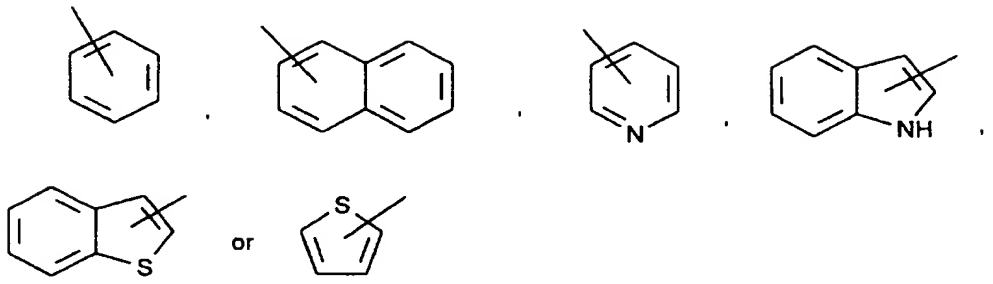


wherein n is 0, 1 or 2, and R^{19} is hydrogen or lower alkyl,



wherein o is an integer selected from the group: 1, 2, 3,

each of R^{11} and R^{12} is independently hydrogen or lower alkyl, or



each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, amino, alkylamino, hydroxy, or the Amadori rearrangement product from an amino group and a hexapyranose or a hexapyranosyl-hexapyranose and

R^{10}, when p is 1, is selected from the group consisting of -H, -COOH, $-CH_2-R^{13}$, $-CO-R^{13}$ or $-CH_2-OH$, wherein

R^{13} is piperazino, morpholino, piperidino, -OH or $-N(R^{14})-R^{15}$, wherein each of R^{14} and R^{15} is independently hydrogen or lower alkyl;

all amide bonds within formula I, that is, between A and B, including G and H, B and C, C and D and D and E may independently be replaced by $-Y-NR^{18}-$, wherein Y is -CO- or $-CH_2-$, and R^{18} is hydrogen, lower alkyl or lower aralkyl; or a pharmaceutically acceptable salt thereof;

for the preparation of a transdermal delivery system, for stimulating the release of growth hormone from the pituitary.

In one embodiment of the above use, the compound of formula I is selected from growth hormone releasing peptides having 3-10 amino acids, preferably 3-9, more preferred 4-8, still more preferred 4-6, and most preferred 5 amino acids, or pharmaceutically acceptable salts thereof.

In another embodiment of the above use, at least one of the amino acids are selected from the group consisting of D-2Nal, D-Phe, Aib, His, Ala, D-Ala, AMB, nipecotic acid or isonipecotic acid.

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In a further embodiment of the above use, A is selected from Aib or 3-AMB, preferably Aib.

In a still further embodiment of the above use G is selected from Ala, 3-aminomethylbenzoyl, R-nipecotinyl, nipecotic acid or isonipecotic acid or G is absent, preferably G is Ala or absent, more preferred G is absent.

In a further embodiment of the above use H is selected from His or Ala, preferably His.

In a still further embodiment of the above use C is selected from D-2Nal, D-Phe or N-Me-D-Phe, preferably D-2Nal.

In a further embodiment of the above use D is selected from D-Phe, D-2Nal or N-Me-D-Phe, preferably D-Phe.

In a still further embodiment of the above use E is selected from Lys-NH_2, D-Lys-NH_2, Lys-OH, D-Lys-OH, Gly-NH_2, Orn-NH_2 or Ser-NH_2, preferably Lys-NH_2, D-Lys-NH_2, Lys-OH, D-Lys-OH or Ser-NH_2, more preferably Lys-NH_2, D-Lys-NH_2 or Ser-NH_2.

In a further embodiment of the above use the compound is selected from the group consisting of

H-Ala-Hisψ(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-His-D-2Nal-D-Phe-Lys-NH_2,
(3-(4-Imidazolyl)propionyl)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Lys-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-His-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-D-2Nal-D-Phe-Lys-NH_2,
(n-Propyl)-His-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-3Pyal-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Phe(4-NH_2)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-His-D-2Nal-D-Phe-Lys-NH_2,
(2-(4-Imidazolyl)acetyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(4-Imidazolyl)acryloyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethyl benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminocrotonoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-Piperidino-carboxyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-NH_2,

(H-Ala-His-D-2Nal-D-Phe-NH)hexane,

6-(H-Ala-His-D-2Nal-D-Phe-NH)hexylamine,

5-(H-Ala-His-D-2Nal-D-Phe-NH)pentylanaine,

H-Ala-His-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys-OH,

(2S)-(H-Ala-His-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2-(H-Ala-His-D-2Nal-D-Phe-NH)ethyl)benzene,

2-(H-Ala-His-D-2Nal-D-Phe-NH)ethylamine,

4-((H-Ala-His-D-2Nal-D-Phe-NH)methyl)benzylamine

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

H-Ala-His-D-2Nal-D-Phe-Phe-NH_2,

H-Ala-His-D-2Nal-D-Phe-D-Phe-NH_2,

H-Ala-His-D-Phe-D-Phe-Lys-NH_2,

H-Ala-His-D-Trp-D-Phe-Lys-NH_2,

H-His-D-2Nal-D-Trp-Lys-NH_2,

H-Ala-His-D-1Nal-D-Phe-Lys-NH_2,

H-Ala-Phe-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

(2R)-(H-Ala-His-D-2Nal-D-Phe-Lys-NH)-3-phenylpropylamine,

H-Ala-N-Me-(2-aminobenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(Methylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-(Aminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-His-Ala-D-2Nal-D-Phe-Lys-NH_2,

4-(H-Ala-His-D-2Nal-D-Phe-NH)butylamine,

3-(H-Ala-His-D-2Nal-D-Phe-NH)propylamine,

(3-(Dimethylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-D-2Nal-D-Phe-Lys-NH_2,

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(3-Aminomethylbenzoyl)-D-hPhe-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)y(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-hPhe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Bzl-Gly-Lys-NH_2,

(2S)-(3-aminomethylbenzoyl)y(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2S)-((3-aminomethylbenzoyl)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-Thial-Lys-NH_2,

(2S)-(H-Aib-Hisy(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-3Pyal-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-F)-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-OMe)-Lys-NH_2,

(2-Aminomethylphenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(2-Aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Phe-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Hisy(CH_2NH)-D-2Nal-D-Phe-Lys-OH,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Gly-NH_2,

H-Aib-His-D-2Nal-D-Phe-Ala-NH_2,

H-Aib-His-D-2Nal-D-Phe-Orn-NH_2,

(5-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-D-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Dab-NH_2,

H-Aib-His-D-2Nal-D-Phey(CH_2NH)-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-N-Me-Lys-NH_2,

(3-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Lys-$N(Me)_2$,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

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(3-Aminomethylbenzoyl)-D-1Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Trp-Lys-NH_2,

(Furfuryl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(2-Pyridylmethyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-3Pyal-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(2-(H-Aib-His-D-2Nal-NH)ethyl)benzene,

N,N-di(2R-Hydroxypropyl)-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(2R-Hydroxypropyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe-N-Me-Lys-NH_2,

H-D-Thr-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Hyp-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phey($CH_2N(Me)$)Lys-NH_2,

3-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

3-((Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3-Aminomethylbenzoyl)-N -Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

3-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

H-Aib-His-D-2Nal-N-Me-D-Phe-Hyp-NH_2,

2-((3-Aminomethylbenzoyl)-

D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

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2-((3R)Piperidinecarbonyl-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane;
2(R)-2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me)-3-phenylpropanol,
3-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,
3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,
3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,
H-Aib-His-D-2Nal-N-Me-D-Phe-Ser-NH_2,
(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH_2,
(4-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,
((3R)-3-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,
(3-Aminomethylbenzoyl)-D-Phe-N-Me-D-Phe-NH_2,
(3-Aminomethylbenzoyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2
((3R)-3-Piperidinecarbonyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,
((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
(2R)-2-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me)-3-(2-naphthyl)propanol,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
3-((3-Aminomethylbenzoyl)-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
(3-aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,
H-Aib-Ala-D-2Nal-N-Me-D-Phe-Lys-NH_2,
H-Aib-His-D-2Nal-N-Me-D-Phe-NH_2,
2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-morpholinoethane,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH-Me,
3-((3-Methylaminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-N-Me_2,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
H-3-Aminomethylbenzoyl-N-Me-D-2Nal-N-Me-D-Phe-NH-CH_3,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NHMe,
and Piperidine-4-carboxylic acid-N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,
or a pharmaceutically acceptable salt thereof.

In a still further embodiment of the above use the pharmaceutically acceptable salt is the besylate, hydrobromide, citrate, sodium, potassium, calcium, zinc, magnisium, meglumine, acetate, benzoate, fumarate, phosphate, malate, maleate, mandelate, mesylate, lactate, salicylate, sulphate, tartrate, succinate, TFA, hydrochloride and/or hydrate.

In a further embodiment of the above use the transdermal delivery system is a iontophoretic delivery system.

In a still further embodiment of the above use the transdermal delivery system further comprises a hydrogel.

In a further embodiment of the above use the transdermal delivery system comprises a dry-state assembly.

In a still further embodiment of the above use the compound is delivered in an amount of from about 0.001 mg to about 10 mg per subject per day.

Due to the lipophilic nature of some amino acids in the compounds of the invention, it would be expected that they have low bioavailability when delivered by the transdermal, preferably the iontophoretic route, however surprisingly the compounds has been shown to posses very high bioavailability when administered transdermally by iontophoresis.

Detailed description of the invention

In the above structural formulas and throughout the present specification, the following terms have the indicated meanings:

The lower alkyl moities specified above are intended to include those alkyl moities, preferably with 1-6 carbon atoms, of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkyl are methyl, ethyl, propyl, butyl, pentyl, and hexyl. Examples of branched alkyl are isopropyl, sec-butyl, tert-butyl, isopentyl, and isohexyl. Examples of cyclic alkyl are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

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The lower alkoxy moities specified above are intended to include those alkoxy moities preferably with 1-6 carbon atoms, of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkyloxy are methoxy, ethoxy, propoxy, butoxy, pentoxy, and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, and isohexoxy. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The lower alkylamino moities specified above are intended to include those alkylamino moities preferably with 1-6 carbon atoms, of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkylamino are methylamino, ethylamino, propylamino, butylamino, pentylamino, and hexylamino. Examples of branched alkylamino are isopropylamino, sec-butylamino, tert-butylamino, isopentylamino, and isohexylamino. Examples of cyclic alkylamino are cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino.

In the present context, the term "aryl" is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected from the group consisting of phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrazinyl, or isothiazolyl, optionally substituted by one or more C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen, amino or aryl. Aryl is preferably phenyl, thienyl, imidazolyl, pyridyl, indolyl, quinoline or naphthyl optionally substituted with halogen, amino, hydroxy, C_{1-6}-alkyl or C_{1-6}-alkoxy.

The lower aralkyl moities specified above are composed of a lower alkyl moity and a aryl moiety, wherein the lower alkyl moiety and aryl moiety are as defined above.

The term "halogen" is intended to include Cl, F, Br and I.

The common three-letter code is used for natural amino acids, e.g. Ala for alanine.

The term "amino acid" or "amino acid residue" is meant to comprise natural L-amino acids or their corresponding D-isomers, or non-natural amino acids such as Ala, Hisy(CH_2NH), D-2Nal, D-Phe, Lys, His, (3-(4-Imidazolyl)propionyl), D-Lys, 5Apent, D-Ala, (n-Propyl)-His, 3Pyal, Phe(4-NH_2), (2-(4-Imidazolyl)acetyl), (3-(4-Imidazolyl)acryloyl), (3-

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Aminomethyl benzoyl), (3-Aminophenylacetyl), (4-Aminophenylacetyl), (3-Aminocrotonoyl), (4-Piperidino-carboxyl), D-Phey(CH_2NH), Lys(maltosyl), Phe, L-2Nal, D-His, D-Trp, Trp, D-1Nal, L-1Nal, N-Me-(2-aminobenzoyl), (3-(Methylaminomethyl)benzoyl), (4-(Aminomethyl)benzoyl), (3-(Dimethylaminomethyl)benzoyl), (3-Amino-3-methylbutanoyl), (3-Aminomethylbenzoyl), D-hPhe, (3-Aminomethylbenzoyl)y(CH_2NH), Gly, D-Thial, Aib, D-3Pyal, D-Phe(4-F), D-Phe(4-OMe), AMB, Orn, Dab, etc.

In a preferred embodiment of the compound of formula I, A is hydrogen, 3-N-Me-AMB, -3-AMB or Aib. When t is 1, G in the compund of formula I is preferably Ala, Gly, sarcosine, 3-aminomethylbenzoyl, R-nipecotinyl, nipecotic acid or isonipecotic acid, more preferably 3-aminomethylbenzoyl, R-nipecotinyl, nipecotic acid or isonipecotic acid. When u is 1, H is preferably His, Phe, Tic, Phe(4-NH_2), 3-Pyal, Gly, Ala, Sar, Pro, Tyr, Arg, Orn, 3-aminomethylbenzoic acid or D-Phe, more preferably H is His, Phe or Ala, most preferably H is His or Ala. C in the compound of formula I is preferably D-2-naphthylalanine (D-2Nal), D-1-naphthylalanine (D-1Nal), D-Phe or D-Trp, more preferably D-2Nal or D-Phe and most preferably N-Me-D-2Nal, D-2Nal, D-Phe, or N-Me-D-Phe. D in the compound of formula I is preferably

D-Phe or D-2Nal. Most preferably D is N-Me-D-Phe-ol, N-Me-D-Phe, N-Me-D-2Nal-ol, N-Me-D-Phe-NH_2, N-Me-D-Phe-NH-Me, or N-Me-D-(4-I)Phe-NH-Me.

When p is 1in the compound of formula I, E is preferably Lys-NH_2, Ser-NH_2, NH-(2-(1-piperazino)ethyl), NH-(3-(1-morpholino)propyl), NH-(2-aminoethyl), NH-(4-aminomethylbenzyl), NH-(benzyl), Lys-OH, NH-(1-hydroxy-6-amino-2S-hexyl), NH-(2-(1-methyl-2-pyrrolidinyl)ethyl), or 3-N,N-dimethyl-aminopropyl, most preferably E is NH-(2-(1-methyl-2-pyrrolidinyl)ethyl), 3-N,N-dimethyl-aminopropyl, Lys-NH_2, or Ser-NH_2

or R^4 in the compound of formula I is preferably 2-naphthyl. R^5 is preferably phenyl. v is preferably 2-6, and R^9 is NH_2 ,2-morpholinoethyl , 3-morpholinopropyl or (1-methylpyrrolidinyl)ethyl. R^{10} is preferably -COOH, -CH_2-OH, -H, -$CONH_2$ or -$CON(CH_3)_2$.

Drugs can be delivered into the systemic circulation via the human skin membrane with low daily doses because first pass hepatic metabolism is avoided (Todd P.A. & Goa K.L., Drugs

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40(4): p. 583-607 (1990)). This may be convenient because low-dose forms may avoid some of the side effects of higher dose oral therapy.

To those skilled in the art, it is well known that the current and potential uses of growth hormone in humans are varied and multitudinous. It is anticipated that, compounds of formula I can be administered for purposes stimulating release of growth hormone from the pituitary gland and would then have similar effects or uses as growth hormone itself. The uses of growth hormone may be summarized as follows: stimulation of growth hormone release in the elderly; prevention of catabolic side effects of glucocorticoids, treatment of osteoporosis, stimulation of the immune system, acceleration of wound healing, accelerating bone fracture repair, treatment of growth retardation, treating renal failure or insufficiency resulting from growth retardation, treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with the Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients, treatment of osteochondrodysplasias, Noonan's syndrome, schizophrenia, depressions, Alzheimer's disease, delayed wound healing and psychosocial deprivation, treatment of pulmonary dysfunction and ventilator dependency, attenuation of protein catabolic responses after major surgery, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis, adjuvant treatment for ovulation induction; to stimulate thymic development and prevent the age-related decline of thymic function, treatment of immunosuppressed patients, improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly, stimulation of osteoblasts, bone remodelling and cartilage growth, stimulation of the immune system in companion animals and treatment of disorder of aging in companion animals, growth promoter in livestock and stimulation of wool growth in sheep.

The daily dose of the peptides of the invention are from 0.001-10 mg/subject, preferably from 0.03-2 mg/subject.

By the term effective amount it is understood that such an amount is sufficient to provide the desired result, that is, prevention or treatment of the above mentioned diseases/disorders.

In this regard, transdermal delivery systems deliver an amount of from about 0.001 mg to about 10 mg per subject per day of the peptides of the invention.

Preferred Embodiments of the invention

A preferred embodiment of the present invention is shown in Figure 1.

Figure 1 is a schematic view of a iontophoretic delivery device for delivering a beneficial agent, that is a compound of formula I of the present invention, through a body surface such as intact skin or a mucosal membrane. Iontophoretic delivery device includes a donor electrode (Ag) assembly 1 and a counter electrode assembly 2. The donor electrode assembly 1 and the counter electrode (AgCl/Ag) assembly 2 are physically attached to insulator 3 and form a single self-contained unit. Insulator 3 prevents the electrode assemblies 1 and 2 from short circuiting the body by preventing electrical and/or ion transport between the electrode assemblies 1 and 2. Electrode assemblies 1 and 2 are connected in series, by appropriate electrical conductors, with an electrical power source. The power source and the electrical conductors are schematically shown as layer 4. The power source used to power the device is typically one or more low voltage batteries. A water impermeable backing layer 5 preferably covers layer 4 with its associated electrical components.

The donor electrode assembly 1 includes an electrode layer 6 and a reservoir layer 7. The reservoir 7 contains the beneficial agent to be iontophoretically delivered by the device. A rate controlling membrane layer 8 is optionally positioned between the reservoir layer 7 and the body surface for controlling the rate at which the agent is delivered to the body sorface or for preventing the delivery of agent to the body surface when the device is turned off. Counter electrode assembly 2 contacts the body surface at a location spaced apart from electrode assembly 1. Counter electrode assembly 2 includes an electrode layer 9 and a reservoir layer 10. The device can be adhered to the body surface by means of ion-conducting adhesive layers 11 and 12. As an altenative to the ion-conducting adhesive layers 11 and 12 shown in Figure 1, the device may be adhered to the body surface using an adhesive overlay. Any of

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the conventional adhesive overlays used to secure passive transdermal delivery devices to the skin may be used.

When the device is in storage, no current flows because the device does not form a closed circuit. When the device is placed on the skin or mucosal membrane of a patient and the electrode assemblies 1 and 2 are sufficiently hydrated to allow ions to flow though the various layers of electrode assemblies 1 and 2, the circuit between the electrodes is closed and the power source begins to deliver current through the device and through the body of the patient. The donor and counter electrode assemblies 1 and 2 normally include a strippable release liner, not shown, which is removed prior to application of electrode assemblies 1 and 2 to a body surface.

As shown in Figure 1, the donor electrode assembly 1 includes a preformed passageway 13 extending though the impermeable backing layer 5, the electronic component layer 4 and the donor electrode layer 6. The donor electrode assembly 1 optionally includes a layer 14 of a liquid-wicking material. Any liquid introduced through passageway 13 is quickly absorbed by layer 14 and wicked across the entire top surface of agent reservoir 7. Preferably, the passageway 13 is also filled with a similar liquid-wicking material. The passageway 13, optionally with the wicking layer 14, enables a liquid to be introduced through passageway 13 form the exterior of the device directly into the matrix of reservoir layer 7 in order to hydrate the matrix and optionally to hydrate the layers 14, 8 and/or 11 if they are present, and to activate the donor electrode assembly 1. In most cases the liquid used to hydrate the matrix of reservoir 7 will be water, but other liquids including non-aqueous liquids, can also be sued to "hydrate" (i.e., activate) the matrix of reservoir layer 7. In the typical case where the liquid is water, the matrix of reservoir layer 7 will be at least partly composed of a hydrophilic material such as hydrophilic polymer, a cellulosic sponge or pad, or other water retaining material. Most preferably, the matrix of reservoir layer 7 will be at least partly composed of a hydrophilic polymer of the type described hereinafter.

Similarly, a preformed passageway 15 extends through the electrode layer 9, the electronic component layer 4 and the impermeable backing layer 5. An optional liquid wicking layer 16 may be provided between reservoir 10 and electrode 9 in counter electrode assembly 2. Wicking layer 16 has a similar function to wicking layer 14 in the donor electrode assembly 1. Passageway 15 and wicking layer 16 establish fluid communication between the exterior of

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the device and the non-hydrated matrix of reservoir layer 10. The passageway 15, optionally with the wicking layer 16, enables a liquid to be introduced through passageway 15 from the exterior of the device directly into the matrix of reservoir layer 10 in order to hydrate the matrix, and optionally to hydrate the layers 16 and/or 12 of there are present, and to activate the counter electrode assembly 2. As with the donor electrode assembly 1, the liquid used to hydrate the matrix of reservoir layer 10 will typically be water, although other liquids including non-aqueous liquids, can also be used.

Preferably, removable plugs (not shown) are provided to seal the openings to passageways 13 and 15, respectively. The plugs may be formed of a material such as wax, rubber, polymer resin or a similar material which is effective to form a seal with passageways 13 and 15.

In accordance with the present invention, at least one of electrode assemblies 1 and 2, and preferably both electrode assemblies 1 and 2 are initially in a substantially dry state. Thus, the various ion transporting layers making up electrode assemblies 1 and 2 are initially in a non-hydrated condition. As used herein, the terms "dry state" and "non-hydrated" mean that the particular layer contains an insufficient amount of liquid to permit ion transport therethrough. For example, the ion transmitting layers of donor electrode assembly 1 include reservoir layer 7 and optional layers 11, 8, and 14. In order for donor electrode assembly 1 to be considered a "dry state" electrode, none of layers 7, 11, 8 and 14 are sufficiently hydrated to allow ion transport therethrough.

Similarly, in order for counter electrode assembly 2 to be considered a "dry state" electrode, neither reservoir layer 10 nor optional layers 12 and 16 contains sufficient liquid to allow ion transport therethrough.

In order to be considered "non-hydrated", reservoir layers 7 and 10 should generally contain less than about 10 wt% liquid, preferably less than about 5 wt% liquid and most preferably less than about 1 wt% liquid.

In order to activate delivery the device, reservoir layers 7 and 10, as well as the optional adhesive layers 11 and 12 and membrane layer 8, must become sufficiently hydrated to enable agent to be transported therethrough by iontophoresis. In order to hydrate reservoir layers 7 and 10, as well as the optional adhesive layers 11 and 12 and membrane layer 8, a liquid

(typically water) is introduced through passageways 13 and 15. As shown in Figure 1, passageways 13 and 15 pass completely through the outer backing layer 5, the electronic component layer 4 and the electrode layers 6 and 9, respectively. Thus, the liquid can be introduced into passageways 13 and 15 simply by pouring the liquid directly into the openings of passageways 13 and 15 in the top of the device.

In most cases, the liquid introduced into the device through passageways 13 and 15 will be composed at least in part of water. However, it is well within the scope of the present invention to "hydrate" the reservoir layers 7 and 10 using other liquids including non-aqueous liquids such as alcohols and glycols. Accordingly, as used herein, the term "hydrate" refers to the addition of either aqueous or non-aqueous based liquids through passageways 13 and 15. Furthermore, in those instances where the non-hydrated reservoir layers 7 and/or 10 initially contain no drug or electrolyte, the hydrating liquid may comprise a liquid solution or suspension of the drug or electrolyte.

Another preferred embodiment of the invention concerns a device for iontophoretically delivering compounds of formula I is constructed as follows. The donor electrode assembly has a multilaminate construction including a zinc foil donor electrode, a polyethylene oxide based electrolyte reservoir, a cellulose acetate selectively permeable membrane and a polyvinyl pyrrolidone based drug reservoir.

The drug reservoir is made by dry blending 65 parts by weight of powdered polyvinyl pyrrolidone having a weight average molecular weight of 360,000 (PVP-K90 manufactured by GAF Corporation) and 35 parts by weight of a compound of formula I at 65°C using a Brabender mixer. The mixture is extruded into a sheet having a thickness of 6 mils and a square section having an area of 5 cm^2 is cut.

An electrolyte reservoir is made by dry blending 70 parts by weight of polyethylene oxide (Polyox® manufactured by Union Carbide of New York, NY) and 30 parts by weight of cholestyramine chloride salt. The cholestyramine cation has a molecular weight of more than 100,000 daltons. The mixture is extruded into a sheet having a thickness of 6 mils and a square sections having an area of 5 cm^2 is cut.

The selectively permeable membrane is made by mixing 90 parts by weight cellulose acetate (CA 398-10 manufactured by FMC Corp. of Philadelphia, PA); and 10 parts by weight of polyethylene glycol (PEG 400 manufactured by Union Carbide of Long Beach, CA) in a Hobart mixer with methylene chloride solvent. The mixture is solvent cast into a sheet having a thickness of 3 mils. A 5 cm^2 square section of the cast sheet is cut. The area resistance of the membrane is about 2 kohm-cm^2. The membrane is freely permeable to ionic species having a molecular weight of less than about 100 daltons. For the high molecular weight ions of a compound of formula I, the membrane exhibits an R_{mass} of about 0.02. The transference number, t, for cholestyramine through the hydrated cellulose acetate membrane is less than about 0.01.

The drug reservoir and the electrolyte reservoir are laminated onto opposite sides of the selectively permeable membrane using heat and pressure. Thereafter, the zinc foil electrode is laminated onto the free surface of the electrolyte reservoir using heat and pressure.

The counter electrode assembly is made by dry blending 70 parts by weight of sodium polyacrylate (Acoflock A-130 manufactured by Mitsui Cyanamide Co.) and 30 parts by weight of sodium chloride at 65°C using a Brabender mixer. The mixture is extruded as a film having a thickness of 6 mils. A square section of the film having an area of 5 cm^2 is cut. A sintered Ag/AgCl disk having an area of 5 cm^2 is laminated onto one side of the polyacrylate film.

The zinc foil donor electrode and the Ag/AgCl counter electrode are electrically connected to an electrical power source which supplies a constant level of direct current of 500 μA or 100 μA/cm^2. The zinc electrode is connected to the positive terminal of the power supply and the Ag/AgCl electrode is connected to the negative terminal. The entire device is adhered to a body surface using a conventional transdermal type adhesive overlay comprising a flexible polyethylene sheet having a peripheral silicone based adhesive.

During operation of the device, both the drug cation (compounds of formula I, molecular weight in the range 300-1500 daltons) and the eletrolyte cation (cholestyramine, molecular weight >100,000 daltons) are substantially unable to penetrate through the cellulose acetate membrane. As the ions of the compound of formula I are driven into the body, the drug counter ions (i.e., chloride ions) pass through the semipermeable membrane and into the

electrolyte reservior. Because the electrolyte cations (i.e., the cholestyramine ions) are unable to penetrate the selectively permeable cellulose acetate membrane, they do not pass into the drug reservoir where they would otherwise undesirably compete with the ions of the compound of formula I for delivery into the body. Therefore a higher percentage of the applied current is carried by ions of the compound of formula I being transported into the body, thereby increasing the transference number for ions of the compound of formula I and the compound of formula I delivery efficiency of the device.

A further embodiment of the drug delivery system of the invention is disclosed below.

The efficiency of compound of formula I (active agent) delivery of an iontophoretic device employing an ionomeric hydrogel can be enhanced by selecting an ionomeric species which has the same charge as the active agent to be delivered. If the active agent is a cation then the ionomeric component of the skin contact layer is cationic. If the active agent is an anion then the ionomeric component is anionic. By selecting an ionomer which has the same charge as the active agent ion, the counter-ion to the ionomer will be opposite in charge of the active agent ion and will not compete with the active agent ion for transport. In addition, since the active agent ion and ionomer have the same charge, any tendency of the active agent ion to "associate", "interact", or "bind" to the ionomeric polymeric component will be minimized due to electrostatic repulsion.

In one example, the carrier layer of polyvinyl pyrrolidone, polyvinyl alcohol and glycerol contains a salt of the compound of formula I. The ionomeric component of the skin contact layer is selected to be a cationic ionomer such as MAPTAC. This ionomer belongs to the class of compounds known as quaternary ammonium salts. To achieve the desired physical properties of the skin contact layer, the MAPTAC is preferably copolymerized or blended with nonionic components such as HEMA or PVA.

When the carrier layer and the skin contact layer come into contact, the compound of formula I migrates into the ionomeric hydrogel of the skin contact layer and forms a loaded hydrogel.

The ionomeric component of the hydrogel is MAPTAC, and has a chloride counter-ion. In a preferred embodiment, the anode contacting the element is silver. Oxidation of silver during

iontophoresis would lead to the formation of insoluble silver chloride. This process minimizes migration of silver into the hydrogel and/or skin. The chloride ion in this example can be supplied as the counter-ion of the active agent and/or as the counter-ion of the ionomeric component.

A still further embodiment of the drug delivery system of the invention is disclosed below.

The compounds of formula I are available in the "free-base" or "alkaloid" or "base" form. Use of this form of active agent may be commercially practical due to availability, or may be preferred due to free-base stability.

The compound of formula I which is sparingly soluble in water as the free-base form, can be incorporated in the carrier layer, of polyvinyl pyrrolidone, glycerol and hyroxypropyl cellulose. The skin contact layer would contain an acidic excipient or combination of acidic ingredients (e.g., hydrochloric, sulfuric, nitric, acetic, tartaric, citric and the like). When contact is made between the adhesive and carrier layers, the compound of formula I (N), is converted to ionic compound of formula I via reaction with the acidic excipient. If hydrogen chloride is used, the reaction

$$N + HCl \longrightarrow HN^{+} + Cl^{-}$$

would occur. As a result, the skin contact layer becomes "loaded" with compound of formula I cation and chloride counter-ion. Preferably the acid content of the first layer would be sufficient to convert all active agent base in the carrier layer to the ionic form. In this example, use of a silver anode would result in the formation of silver chloride due to the presene of the chloride counter-ion.

A further embodiment of the drug delivery system of the invention is disclosed below.

This embodiment achieves the same advantages as the above embodiment, but by use of an acidic polymer rather than the combination of an acidic excipient and cationic polymer as above. The carrier layer of polyvinyl alcohol and hydromethyl cellulose contains the compound of formula I and the first hydrogel layer contains the acidic polymer, H-AMPS. Prefe-

rably the acid content of the first layer is sufficient to convert all of the compound of formula I to salt in the carrier layer, but not in great excess.

When contact is established between the adhesive and carrier layers, the compound of formula I reacts with the H-AMPS to form the hydromorphone cation:

$$M + HAMPS \longrightarrow HM^{+} + AMPS^{-}$$

The addition of chloride to this reservoir can be accomplished by either of two methods. First, an acidic excipient and the acidic polymer would preferably be sufficient to convert all compound of formula I , but not in great excess.

The total amount of hydromorphone in the active element is determined by the therapeutic dose rate and duration of use of the iontophoretic device. To achieve the proper acid content of the skin contact layer and the appropriate total active agent content of the element overall (i.e., little or no excess active agent), or to achieve other preferred physical properties (e.g., flexibility, tackiness, shear strength etc.) nonionic polymers can be added to the skin contact layer.

For example, the adhesive hydrogel layer may contain H-AMPS blended with PVA, or H-AMPS copolymerized with HEMA. The ratio of acidic polymer to nonionic polymer is determined, by the amount of alkaloid in the carrier layer and by the acid content of the skin contact layer needed for conversion of the alkaloid to drug cation.

In general, conversion of a compound of formula I or free-base drug in the carrier layer to a drug cation is accomplished by an acid-containing skin contact layer. The acid content of the skin contact layer can be provided by acidic excipients and/or acidic-polymer alone or in combination with nonionic polymers and/or cationic polymers as described above, provided that

(1) conversion of compound of formula I base to drug cation is achieved;
(2) co-ion competition is minimized, and
(3) preferably that an appropriate counter-ion is present considering the nature of the electrochemical reaction at the anode (e.g., chloride for a silver anode).

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The above embodiments should by no means be construed as limiting the invention.

Example 1

Polyvinyl alcohol and components capable of containing large amount of water were evenly mixed. The mixture was dispersed well by adding purified water portionwise at 60-70°C until a homogenous aqueous liquid is obtained. This aqueous liquid was poured in a casting mold and frozen at -20°C overnight. The frozen mass was then thawed at ambient temperature to give a hydrogel.

NNC is H-Aib-His-D-2Nal-D-Phe-D-Lys-NH_2.

Component	Amount
Polyvinyl alcohol (degree of polymerization 2000, degree of saponification 99%)	5 g
Sodium hyaluronate	0.5 g
NNC	10 g
Purified water	100 g

Using the above formula, a hydrogel was prepared by the method described hereinbefore.

Example 2

Component	Amount
Polyvinyl alcohol (degree of polymerization 2000, degree of saponification 99%)	4.5 g
Curidan (β-1,3-glucan; manufactured by Takeda chemical industries, Ltd.)	0.5 g
Sodium hyaluronate	0.5 g
NNC	10 g
Sodium citrate	50 mg
Purified water to make	100 g

Using the above formula, a hydrogel was prepared by the described method.

Example 3

Component	Amount
Polyvinyl alcohol (degree of polymerization 1700, degree of saponification 95%)	12 g
Polyvinyl alcohol (degree of polymerization 2500, degree of saponification 99%)	0.5 g
Curdlan	1.0 g
Sodium hyaluronate	0.2 g
NNC	10 g
Purified water to make	100 g

Using the above formula, a hydrogel was prepared by the described method.

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Example 4

Component	Amount
Polyvinyl alcohol (degree of polymerization 2000, degree of saponification 99%)	5 g
Sumikagel SP 510 (a sodium salt of hydrolyzed copolymer composed of vinyl acetate and methyl acrylate; manufactured by Sumitomo Chemical Ltd.)	0.5 g
NNC	5 g
Purified water	100 g

Using the above formula, a hydrogel was prepared by the described method.

CLAIMS

1. A drug delivery system comprising

a) a transdermal device, and

b) as an active agent, a compound of the general formula I

$$A\text{-}B\text{-}C\text{-}D(\text{-}E)_p \quad (I)$$

wherein p is 0 or 1;

A is hydrogen or $R^1\text{-}(CH_2)_q\text{-}(X)_r\text{-}(CH_2)_s\text{-}CO\text{-}$, wherein

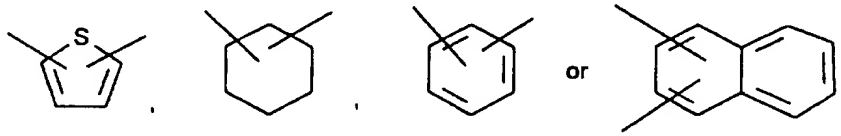
q is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

r is 0 or 1;

s is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

R^1 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino or $N(R^2)$-R^3, wherein each of R^2 and R^3 is independently hydrogen or lower alkyl optionally substituted by one or more hydroxyl, pyridinyl or furanyl groups; and

X, when r is 1, is -NH-, $-CH_2$-, -CH=CH-, $-C(R^{16})(R^{17})$-,



wherein each of R^{16} and R^{17} is independently hydrogen or lower alkyl;

B is $(G)_t\text{-}(H)_u$ wherein each of t and u independently is 0 or 1;

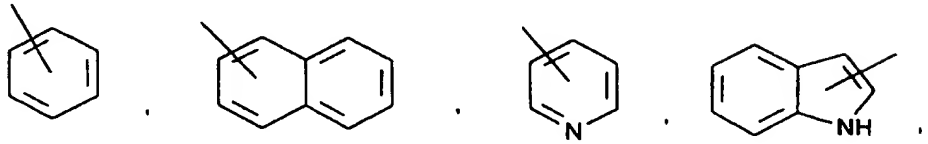
G and H are amino acid residues selected from the group consisting of natural L-amino acids or their corresponding D-isomers, or non-natural amino acids such as 1,4-diaminobutyric acid, amino-isobutyric acid, 1,3-diaminopropionic acid, 4-aminophenylalanine, 3-pyridylalanine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydronorharman-3-carboxylic acid, N-methylanthranilic acid, anthranilic acid, N-benzylglycine, 3-aminomethylbenzoic acid, 3-amino-3-methyl butanoic acid, sarcosine, nipecotic acid or iso-nipecotic acid;

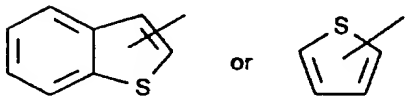
and wherein, when both t and u are 1, the amide bond between G and H is optionally replaced by $Y\text{-}NR^{18}$-, wherein Y is -CO- or $-CH_2$-, and R^{18} is hydrogen, lower alkyl or lower aralkyl;

C is a D-amino acid of formula -NH-CH($(CH_2)_w$-R^4)-CO- wherein

w is 0, 1 or 2; and

R^4 is selected from the group consisting of





each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, lower alkylamino, amino or hydroxy;

D, when p is 1, is a D-amino acid of formula

-NH-CH($(CH_2)_k$-R^5)-CO-

or, when p is 0, D is -NH-CH($(CH_2)_l$-R^5)-CH_2-R^6

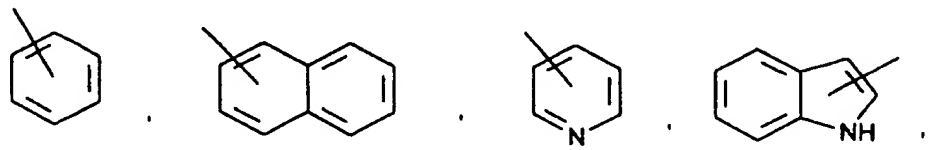
or -NH-CH($(CH_2)_m$-R^5)-CO-R^6, wherein

k is 0, 1 or 2;

l is 0, 1 or 2;

m is 0, 1 or 2;

R^5 is selected from the group consisting of



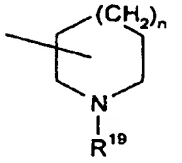
each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy amino or hydroxy; and

R^6 is piperazino, morpholino, piperidino, -OH or -N(R^7)-R^8, wherein each of R^7 and R^8 is independently hydrogen or lower alkyl;

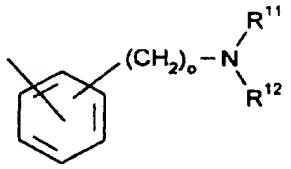
E, when p is 1, is -NH-CH(R^{10})-$(CH_2)_v$-R^9, wherein

v is 0 or an integer selected from the group: 1, 2, 3, 4, 5, 6, 7, 8;

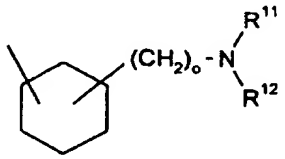
R^9 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino, -N(R^{11})-R^{12}, or



wherein n is 0, 1 or 2, and R^{19} is hydrogen or lower alkyl,

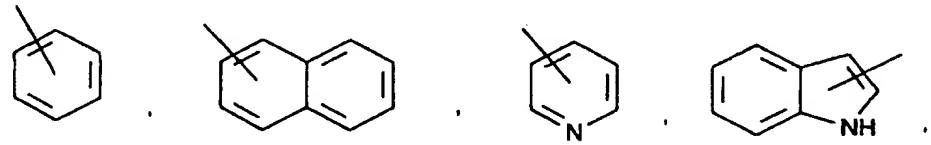


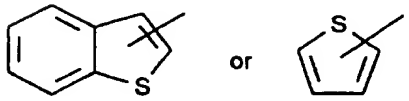
or



wherein o is an integer selected from the group: 1, 2, 3,

each of R^{11} and R^{12} is independently hydrogen or lower alkyl, or





or

each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, amino, alkylamino, hydroxy, or the Amadori rearrangement product from an amino group and a hexapyranose or a hexapyranosyl-hexapyranose and

R^{10}, when p is 1, is selected from the group consisting of -H, -COOH, -CH_2-R^{13},

-CO-R^{13} or -CH_2-OH, wherein

R^{13} is piperazino, morpholino, piperidino, -OH or -N(R^{14})-R^{15}, wherein each of R^{14} and R^{15} is independently hydrogen or lower alkyl;

all amide bonds within formula I, that is, between A and B, including G and H, B and C, C and D and D and E may independently be replaced by -Y-NR^{18}-, wherein Y is -CO- or -CH_2-, and R^{18} is hydrogen, lower alkyl or lower aralkyl; or a pharmaceutically acceptable salt thereof.

2. The drug delivery system according to claim 1, wherein said compound of formula I is selected from growth hormone releasing peptides having 3-10 amino acids, preferably 3-9, more preferred 4-8, still more preferred 4-6, and most preferred 5 amino acids, or pharmaceutically acceptable salts thereof.

3. The drug delivery system according to claim 2, wherein, at least one of the amino acids are selected from the group consisting of D-2Nal, D-Phe, Aib, His, Ala, D-Ala, AMB, nipecotic acid or isonipecotic acid.

4. The drug delivery system according to claim 2 and 3, wherein A is selected from Aib or 3-AMB, preferably Aib.

5. The drug delivery system according to claim 2 and 3 or 4, wherein G is selected from Ala, 3-aminomethylbenzoyl, R-nipecotinyl, nipecotic acid or isonipecotic acid or G is absent, preferably G is Ala or absent, more preferred G is absent.

6. The drug delivery system according to claim 2 and 3 or 4 or 5, wherein H is selected from His or Ala, preferably His.

7. The drug delivery system according to claim 2 and 3 or 4, 5 or 6, wherein C is selected from D-2Nal, D-Phe or N-Me-D-Phe, preferably D-2Nal.

8. The drug delivery system according to claim 2 and 3 or 4, 5, 6 or 7, wherein D is selected from D-Phe, D-2Nal or N-Me-D-Phe, preferably D-Phe.

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9. The drug delivery system according to claim 2 and 3 or 4, 5, 6, 7 or 8, wherein E is selected from Lys-NH_2, D-Lys-NH_2, Lys-OH, D-Lys-OH, Gly-NH_2, Orn-NH_2 or Ser-NH_2, preferably Lys-NH_2, D-Lys-NH_2, Lys-OH, D-Lys-OH or Ser-NH_2, more preferably Lys-NH_2, D-Lys-NH_2 or Ser-NH_2.

10. The drug delivery system according to claim 1, 2, 3, 4, 5, 6, 7, 8 or 9, wherein said compound is selected from the group consisting of

H-Ala-Hisψ(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-His-D-2Nal-D-Phe-Lys-NH_2,
(3-(4-Imidazolyl)propionyl)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Lys-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-His-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-D-2Nal-D-Phe-Lys-NH_2,
(n-Propyl)-His-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-3Pyal-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Phe(4-NH_2)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-His-D-2Nal-D-Phe-Lys-NH_2,
(2-(4-Imidazolyl)acetyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-(4-Imidazolyl)acryloyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-Aminomethyl benzoyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,
(4-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,
(3-Aminocrotonoyl)-D-2Nal-D-Phe-Lys-NH_2,
(4-Piperidino-carboxyl)-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-His-D-2Nal-D-Phe-NH_2,
(H-Ala-His-D-2Nal-D-Phe-NH)hexane,
6-(H-Ala-His-D-2Nal-D-Phe-NH)hexylamine,
5-(H-Ala-His-D-2Nal-D-Phe-NH)pentylanaine,
H-Ala-His-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,
H-Ala-His-D-2Nal-D-Phe-Lys-OH,
(2S)-(H-Ala-His-D-2Nal-D-Phe-NH)-6-aminohexanol,

SUBSTITUTE SHEET (RULE 26)

(2-(H-Ala-His-D-2Nal-D-Phe-NH)ethyl)benzene,

2-(H-Ala-His-D-2Nal-D-Phe-NH)ethylamine,

4-((H-Ala-His-D-2Nal-D-Phe-NH)methyl)benzylamine ,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

H-Ala-His-D-2Nal-D-Phe-Phe-NH_2,

H-Ala-His-D-2Nal-D-Phe-D-Phe-NH_2,

H-Ala-His-D-Phe-D-Phe-Lys-NH_2,

H-Ala-His-D-Trp-D-Phe-Lys-NH_2,

H-His-D-2Nal-D-Trp-Lys-NH_2,

H-Ala-His-D-1Nal-D-Phe-Lys-NH_2,

H-Ala-Phe-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

(2R)-(H-Ala-His-D-2Nal-D-Phe-Lys-NH)-3-phenylpropylamine,

H-Ala-N-Me-(2-aminobenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(Methylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-(Aminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-His-Ala-D-2Nal-D-Phe-Lys-NH_2,

4-(H-Ala-His-D-2Nal-D-Phe-NH)butylamine,

3-(H-Ala-His-D-2Nal-D-Phe-NH)propylamine,

(3-(Dimethylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-hPhe-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)y(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-hPhe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Bzl-Gly-Lys-NH_2,

(2S)-(3-aminomethylbenzoyl)y(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2S)-((3-aminomethylbenzoyl)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-Thial-Lys-NH_2,

(2S)-(H-Aib-Hisy(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-3Pyal-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-F)-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-OMe)-Lys-NH_2,

(2-Aminomethylphenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

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(2-Aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Phe-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Hisy(CH_2NH)-D-2Nal-D-Phe-Lys-OH,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Gly-NH_2,

H-Aib-His-D-2Nal-D-Phe-Ala-NH_2,

H-Aib-His-D-2Nal-D-Phe-Orn-NH_2,

(5-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-D-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Dab-NH_2,

H-Aib-His-D-2Nal-D-Phey(CH_2NH)-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-N-Me-Lys-NH_2,

(3-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Lys-N(Me)$_2$,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-1Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Trp-Lys-NH_2,

(Furfuryl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(2-Pyridylmethyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-3Pyal-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(2-(H-Aib-His-D-2Nal-NH)ethyl)benzene,

N,N-di(2R-Hydroxypropyl)-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(2R-Hydroxypropyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-D-Phe-Lys-NH_2,

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(3-Aminomethylbenzoyl)-D-2Nal-D-Phe-N-Me-Lys-NH_2,

H-D-Thr-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Hyp-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phey(CH_2N(Me))Lys-NH_2,

3-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

3-((Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3-Aminomethylbenzoyl)-N -Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

3-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

H-Aib-His-D-2Nal-N-Me-D-Phe-Hyp-NH_2,

2-((3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane, 2-((3R)Piperidinecarbonyl-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2- pyrrolidinyl)ethane;

2(R)-2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me)-3-phenylpropanol,

3-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

H-Aib-His-D-2Nal-N-Me-D-Phe-Ser-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH_2,

(4-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,

((3R)-3-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,

(3-Aminomethylbenzoyl)-D-Phe-N-Me-D-Phe-NH_2,

(3-Aminomethylbenzoyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2

((3R)-3-Piperidinecarbonyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

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(2R)-2-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me)-3-(2-naphthyl)propanol,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
3-((3-Aminomethylbenzoyl)-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
(3-aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,
H-Aib-Ala-D-2Nal-N-Me-D-Phe-Lys-NH_2,
H-Aib-His-D-2Nal-N-Me-D-Phe-NH_2,
2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-morpholinoethane,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH-Me,
3-((3-Methylaminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-N-Me_2,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
H-3-Aminomethylbenzoyl-N-Me-D-2Nal-N-Me-D-Phe-NH-CH_3,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NHMe,
and Piperidine-4-carboxylic acid-N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,
or a pharmaceutically acceptable salt thereof.

11. The delivery system according to any one of claims 1-10 wherein the pharmaceutically acceptable salt is the besylate, hydrobromide, citrate, sodium, potassium, calcium, zinc, magnisium, meglumine, acetate, benzoate, fumarate, phosphate, malate, maleate, mandelate, mesylate, lactate, salicylate, sulphate, tartrate, succinate, TFA, hydrochloride and/or hydrate.

12. The drug delivery system according to any one of the claims 1-11, wherein said transdermal device is a iontophoretic device.

13. The delivery system according to any one of the claims 1-12 which further comprises a hydrogel.

14. The delivery system according to any one of the claims 1-12 wherein said transdermal device comprises a dry-state assembly.

15. The delivery system according to any one of the claims 1-14, wherein said compound is delivered in an amount of from about 0.001 mg to about 10 mg per subject per day.

16. Use of a compound of the general formula I

wherein p is 0 or 1;

A is hydrogen or R^1-$(CH_2)_q$-$(X)_r$-$(CH_2)_s$-CO-, wherein

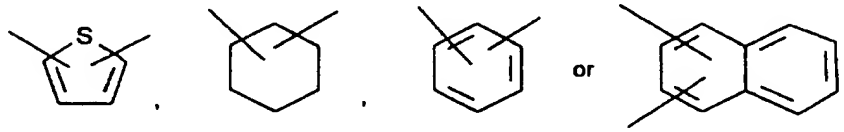
q is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

r is 0 or 1;

s is 0 or an integer selected from the group: 1, 2, 3, 4, 5;

R^1 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino or N(R^2)-R^3, wherein each of R^2 and R^3 is independently hydrogen or lower alkyl optionally substituted by one or more hydroxyl, pyridinyl or furanyl groups; and

X, when r is 1, is -NH-, -CH_2-, -CH=CH-, -C(R^{16})(R^{17})-,



wherein each of R^{16} and R^{17} is independently hydrogen or lower alkyl;

B is $(G)_t$-$(H)_u$ wherein each of t and u independently is 0 or 1;

G and H are amino acid residues selected from the group consisting of natural L-amino acids or their corresponding D-isomers, or non-natural amino acids such as 1,4-diaminobutyric acid, amino-isobutyric acid, 1,3-diaminopropionic acid, 4-aminophenylalanine, 3-pyridylalanine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 1,2,3,4-tetrahydronorharman-3-carboxylic acid, N-methylanthranilic acid, anthranilic acid, N-benzylglycine, 3-aminomethylbenzoic acid, 3-amino-3-methyl butanoic acid, sarcosine, nipecotic acid or iso-nipecotic acid;

and wherein, when both t and u are 1, the amide bond between G and H is optionally replaced by Y-NR^{18}-, wherein Y is -CO- or -CH_2-, and R^{18} is hydrogen, lower alkyl or lower aralkyl;

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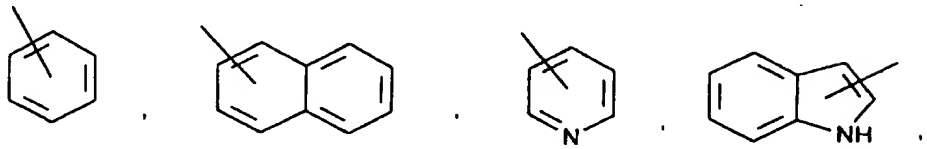
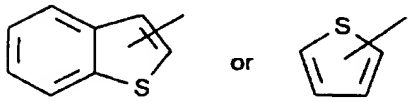
C is a D-amino acid of formula -NH-CH($(CH_2)_w$-R^4)-CO- wherein

w is 0, 1 or 2; and

R^4 is selected from the group consisting of





each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, lower alkylamino, amino or hydroxy;

D, when p is 1, is a D-amino acid of formula

-NH-CH($(CH_2)_k$-R^5)-CO-

or, when p is 0, D is -NH-CH($(CH_2)_l$-R^5)-CH_2-R^6

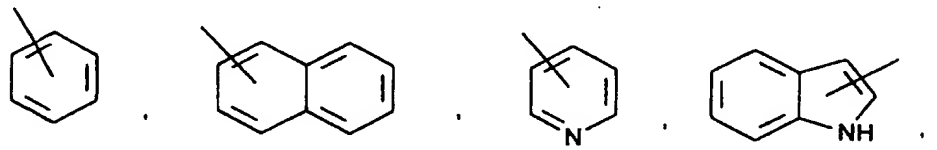
or -NH-CH($(CH_2)_m$-R^5)-CO-R^6, wherein

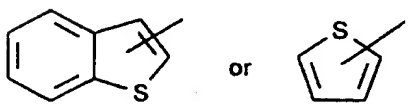
k is 0, 1 or 2;

l is 0, 1 or 2;

m is 0, 1 or 2;

R^5 is selected from the group consisting of





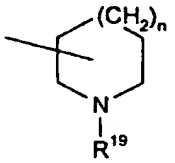
each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy amino or hydroxy; and

R^6 is piperazino, morpholino, piperidino, -OH or -N(R^7)-R^8, wherein each of R^7 and R^8 is independently hydrogen or lower alkyl;

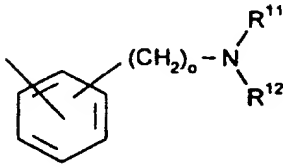
E, when p is 1, is -NH-CH(R^{10})-$(CH_2)_v$-R^9, wherein

v is 0 or an integer selected from the group: 1, 2, 3, 4, 5, 6, 7, 8;

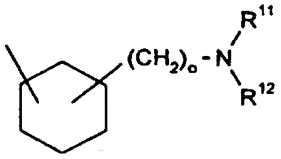
R^9 is hydrogen, imidazolyl, guanidino, piperazino, morpholino, piperidino, -N(R^{11})-R^{12}, or



wherein n is 0, 1 or 2, and R^{19} is hydrogen or lower alkyl,

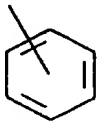


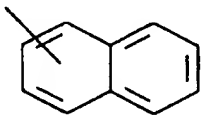
or

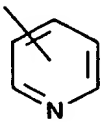


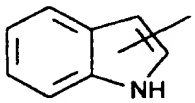
wherein o is an integer selected from the group: 1, 2, 3,

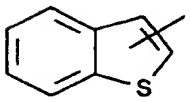
each of R^{11} and R^{12} is independently hydrogen or lower alkyl, or



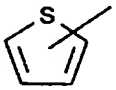








or



each of which is optionally substituted with halogen, lower alkyl, lower alkyloxy, amino, alkylamino, hydroxy, or the Amadori rearrangement product from an amino group and a hexapyranose or a hexapyranosyl-hexapyranose and

R^{10}, when p is 1, is selected from the group consisting of -H, -COOH, -CH_2-R^{13},

-CO-R^{13} or -CH_2-OH, wherein

R^{13} is piperazino, morpholino, piperidino, -OH or -N(R^{14})-R^{15}, wherein each of R^{14} and R^{15} is independently hydrogen or lower alkyl;

all amide bonds within formula I, that is, between A and B, including G and H, B and C, C and D and D and E may independently be replaced by -Y-NR^{18}-, wherein Y is -CO- or -CH_2-, and R^{18} is hydrogen, lower alkyl or lower aralkyl; or a pharmaceutically acceptable salt thereof;

for the preparation of a transdermal device, for stimulating the release of growth hormone from the pituitary.

17. The use according to claim 16, wherein said compound of formula I is selected from growth hormone releasing peptides having 3-10 amino acids, preferably 3-9, more preferred 4-8, still more preferred 4-6, and most preferred 5 amino acids, or pharmaceutically acceptable salts thereof.

18. The use according to claim 17, wherein at least one of the amino acids are selected from the group consisting of D-2Nal, D-Phe, Aib, His, Ala, D-Ala, AMB, nipecotic acid or isonipecotic acid.

19. The use according to claim 16, 17 or 18, wherein said compound is selected from the group consisting of

H-Ala-Hisy(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,
H-Ala-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-His-D-2Nal-D-Phe-Lys-NH_2,
(3-(4-Imidazolyl)propionyl)-D-2Nal-D-Phe-Lys-NH_2,
H-D-Lys-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-His-D-2Nal-D-Phe-Lys-NH_2,
H-D-Ala-D-2Nal-D-Phe-Lys-NH_2,
H-5Apent-D-2Nal-D-Phe-Lys-NH_2,
(n-Propyl)-His-D-2Nal-D-Phe-Lys-NH_2,
H-Ala-3Pyal-D-2Nal-D-Phe-Lys-NH_2,

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H-Ala-Phe(4-NH_2)-D-2Nal-D-Phe-Lys-NH_2,

H-D-Ala-His-D-2Nal-D-Phe-Lys-NH_2,

(2-(4-Imidazolyl)acetyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(4-Imidazolyl)acryloyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethyl benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminocrotonoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-Piperidino-carboxyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-NH_2,

(H-Ala-His-D-2Nal-D-Phe-NH)hexane,

6-(H-Ala-His-D-2Nal-D-Phe-NH)hexylamine,

5-(H-Ala-His-D-2Nal-D-Phe-NH)pentylanaine,

H-Ala-His-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys-OH,

(2S)-(H-Ala-His-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2-(H-Ala-His-D-2Nal-D-Phe-NH)ethyl)benzene,

2-(H-Ala-His-D-2Nal-D-Phe-NH)ethylamine,

4-((H-Ala-His-D-2Nal-D-Phe-NH)methyl)benzylamine

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

H-Ala-His-D-2Nal-D-Phe-Phe-NH_2,

H-Ala-His-D-2Nal-D-Phe-D-Phe-NH_2,

H-Ala-His-D-Phe-D-Phe-Lys-NH_2,

H-Ala-His-D-Trp-D-Phe-Lys-NH_2,

H-His-D-2Nal-D-Trp-Lys-NH_2,

H-Ala-His-D-1Nal-D-Phe-Lys-NH_2,

H-Ala-Phe-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

(2R)-(H-Ala-His-D-2Nal-D-Phe-Lys-NH)-3-phenylpropylamine,

H-Ala-N-Me-(2-aminobenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(Methylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-(Aminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-His-Ala-D-2Nal-D-Phe-Lys-NH_2,

4-(H-Ala-His-D-2Nal-D-Phe-NH)butylamine,

3-(H-Ala-His-D-2Nal-D-Phe-NH)propylamine,

(3-(Dimethylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-hPhe-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)y(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-hPhe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Bzl-Gly-Lys-NH_2,

(2S)-(3-aminomethylbenzoyl)y(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2S)-((3-aminomethylbenzoyl)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-Thial-Lys-NH_2,

(2S)-(H-Aib-Hisy(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-3Pyal-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-F)-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-OMe)-Lys-NH_2,

(2-Aminomethylphenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(2-Aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Phe-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Hisy(CH_2NH)-D-2Nal-D-Phe-Lys-OH,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Gly-NH_2,

H-Aib-His-D-2Nal-D-Phe-Ala-NH_2,

H-Aib-His-D-2Nal-D-Phe-Orn-NH_2,

(5-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-D-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Dab-NH_2,

H-Aib-His-D-2Nal-D-Phey(CH_2NH)-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-N-Me-Lys-NH_2,

(3-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-Me-D-Phe-Lys-NH_2,

ENSDOCID: <WO 9808492A1>

H-Aib-His-D-2Nal-D-Phe-Lys-N(Me)$_2$,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-1Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Trp-Lys-NH_2,

(Furfuryl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(2-Pyridylmethyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-3Pyal-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(2-(H-Aib-His-D-2Nal-NH)ethyl)benzene,

N,N-di(2R-Hydroxypropyl)-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(2R-Hydroxypropyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phey(CH_2NH)Lys-NH_2,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe-N-Me-Lys-NH_2,

H-D-Thr-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Hyp-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phey($CH_2N(Me)$)Lys-NH_2,

3-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

3-((Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-pyrrolidinyl)ethane,

3-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

BNSDOCID: <WO 9808492A1>

H-Aib-His-D-2Nal-N-Me-D-Phe-Hyp-NH_2,

2-((3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-((3R)Piperidinecarbonyl-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane;

2(R)-2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me)-3-phenylpropanol,

3-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

H-Aib-His-D-2Nal-N-Me-D-Phe-Ser-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH_2,

(4-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,

((3R)-3-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2,

(3-Aminomethylbenzoyl)-D-Phe-N-Me-D-Phe-NH_2,

(3-Aminomethylbenzoyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2

((3R)-3-Piperidinecarbonyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

(2R)-2-((3-Aminomethylbenzoyl))-N-Me-D-2Nal-N-Me)-3-(2-naphthyl)propanol,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

3-((3-Aminomethylbenzoyl)-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

(3-aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-Ala-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-Me-D-Phe-NH_2,

2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-morpholinoethane,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH-Me,

3-((3-Methylaminomethylbenzoyl))-N-Me-D-2Nal-N-Me-D-Phe-NH)-N,N-dimethylaminopropane,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-N-Me_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,

H-3-Aminomethylbenzoyl-N-Me-D-2Nal-N-Me-D-Phe-NH-CH_3,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NHMe,

and Piperidine-4-carboxylic acid-N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

or a pharmaceutically acceptable salt thereof.

20. The use according to any one of claims 16-19, wherein the pharmaceutically acceptable salt is the besylate, hydrobromide, citrate, sodium, potassium, calcium, zinc, magnisium, meglumine, acetate, benzoate, fumarate, phosphate, malate, maleate, mandelate, mesylate, lactate, salicylate, sulphate, tartrate, succinate, TFA, hydrochloride and/or hydrate.

21. The use according to any one of the claims 16-20, wherein said transdermal device is a iontophoretic device.

22. The use according to any one of the claims 16-21 wherein said delivery system further comprises a hydrogel.

23. The use according to any one of the claims 16-22 wherein said transdermal device comprises a dry-state assembly.

24. The use according to any one of the claims 16-23, wherein said compound is delivered in an amount of from about 0.001 mg to about 10 mg per subject per day.

BNSDOCID: <WO 9808492A1>

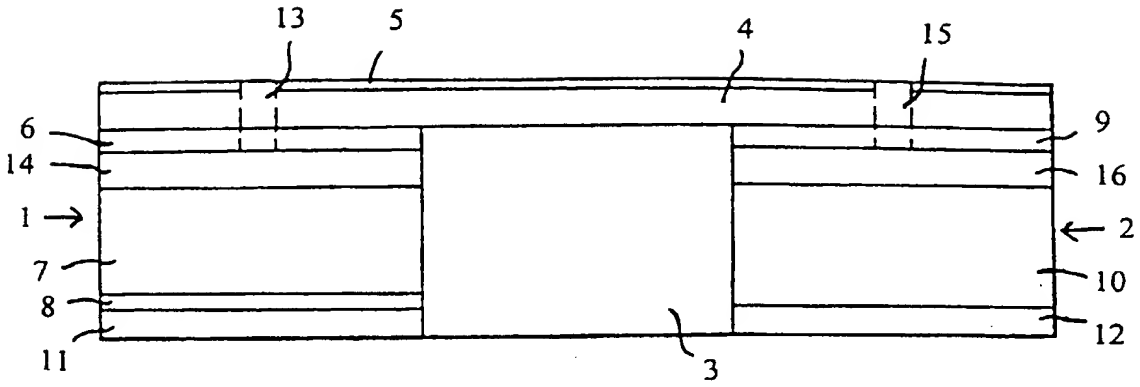

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00346

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/70, A61K 38/08, A61N 1/30
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, USPATFULL, CAPLUS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, File 73, EMBASE, Dialog accession no. 8449374, EMBASE accession no. 92125292, Kumar S. et al: "In vivo transdermal iontophoretic delivery of growth hormone releasing factor GRF (1-44) in hairless guinea pigs", J. Control. Release (Netherlands), 1992, 18/3 (213-220) --	1-24
X	Dialog Information Services, File 73, EMBASE, Dialog accession no. 10042762, EMBASE accession no. 96224449, Green P.G.: "Iontophoretic delivery of peptide drugs", Journal of Controlled Release (Netherlands), 1996, 41/1-2 (33-48) --	1-24

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 1997	19 -12- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

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BNSDOCID: <WO 9808492A1>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00346

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, File 73, EMBASE, Dialog accession no. 7887936, EMBASE accession no. 90319436, Chien Y.W. et al: "Facilitated transdermal delivery of therapeutic peptides and proteins by iontophoretic delivery devices", J. Control. Release (Netherlands), 1990, 13/2-3 (263-278)	1-24
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